**The instinctive human fear of radioactivity is not irrational . . .
it is also so universal and so enduring that it is a political fact of life.**
Peter Pringle and James Spigelman
The Nuclear Barons, 1981

Forum

Of Mice and Humans

Japanese scientists have, for the first time, successfully introduced an intact human chromosome into mouse embryonic stem (ES) cells. This advance, reported in the June 1997 issue of *Nature Genetics*, may make possible medical treatments that are now technically difficult or impossible, and may allow for studies of the function of genes in their native genetic environment.

Kazuma Tomizuka of the Central Laboratories for Key Technology at Kirin Brewery Company, Ltd., in Yokohama, Japan, and nine coauthors described how intact human chromosomes were transferred into the ES cells through a process called microcell-mediated chromosome transfer (MMCT) and used to produce chimeric mice.

The group introduced chromosome 2, 14, or 22 individually into mice. Chromosomes 14 and 22 remained separate and intact, retaining all the genetic information normally contained in those chromosomes. A fragment of chromosome 2 not only remained stable and separate in the genome, but also was passed through the germline to four generations of descendants, showing that the fragment can successfully move through the normal cellular processes of mitosis and meiosis in the mouse cells.

The Japanese scientists chose chromosomes 2, 14, and 22 because these chromosomes contain the genes necessary to produce the heavy and light peptide chains that make up human antibodies. They hoped to produce antibodies that would contain only human proteins, without any proteins of mouse origin. Previous studies have transferred genes to produce human antibodies in mice but, because insufficient genetic material was transferred, the antibodies were created from the genes of both mice and humans. Such antibodies would therefore contain proteins derived from mice as well as humans and, when injected into human patients during gene therapies, would be recognized by the body as foreign and rejected. Theoretically, because MMCT allows for the transfer of whole chromosomes, antibodies produced using this method would contain no mouse proteins, thus circumventing a daunting hurdle in the clinical use of antibodies.

The group showed that the transferred chromosomes are retained intact and express the proteins that are encoded on the chromosome. Not only did the mice produce antibodies (which recombined normally) and use them to launch an attack on an injected antigen, they also expressed the genes mostly in the thymus and spleen, exhibiting tissue-appropriate expression.

Foreign genes have previously been introduced into cells and living organisms by the transfer of yeast artificial chromosomes (YACs) into cells or by using bacterial vector systems. However, this is the first time an entire human chromosome has been transferred into an organism. Tomizuka's group transferred 50 times more DNA than had been previously introduced into a mouse. "The pieces we wanted to use were two to three megabases [long]," said Mitsuo Oshimura, one of the authors of the paper and a scientist in the department of molecular and cell genetics at Tottori University. "That's too big for a YAC."

"Why were we first?" said Oshimura. "Because no one else tried. We, too, were surprised it worked. It was encouraging that YACs can be used, but we jumped into trying to put the whole chromosome in."

By introducing entire chromosomes, the group is providing the human genes the genetic environment they need to be expressed normally in the foreign mouse cells. Genes not only require their own code to be expressed but may also require many regulatory sequences, which sometimes reside thousands of base pairs away from the expressed gene on the chromosome.

Patrick Vojta, a former postdoctoral fellow at the NIEHS whose graduate and postgraduate work included MMCT, said, "This work has taken what was previously a common cell culture model and brought it up to the level of the organism." There is much speculation as to other future uses of this method. It may be useful in studying the normal function of genes. "The ability to make a better mouse [model], one that more closely resembles the human, is a very important goal," said Carl Barrett, scientific director of the NIEHS and a leading expert on MMCT. "The paper by Tomizuki [and colleagues] will greatly facilitate our ability to express human genes in the mouse and thereby improve experimental models of human disease."

The group's next paper, which has been submitted but not yet published, will report the successful simultaneous transfer of two chromosomes into the genome of one mouse, said Oshimura. The researchers plan to extend the work by crossing mice containing human chromosomes with knockout mice that cannot produce mouse antibodies. It is hoped that the resulting offspring will make only human antibodies.

Currently, the group plans to transfer chromosome 21 to produce a mouse model of Down's syndrome, which is caused by trisomy 21. They also hope to transfer the chromosomes containing the human P450 metabolic genes to study the toxicity of chemical metabolites produced by humans when exposed to environmental toxins.

Irradiating Ourselves

Everyone living in the contiguous 48 states during U.S. atomic testing in the 1950s was exposed to radioactive iodine, and these exposures could ultimately cause 10,000–75,000 excess cases of thyroid cancer, according to information released in August by the National Cancer Institute (NCI).

The highest doses of iodine-131, the NCI reports, were probably received by people living in certain areas of Idaho and Montana during the testing. While the average thyroid dose of radiation to the 160 million Americans who were exposed was around 2 rads, the dose to people living in Meagher County, Montana, and Custer, Gem, Blaine, and Lemhi counties in Idaho was between 12 and 16 rads. The average individual in the United States today is exposed to about 0.1 rad per year of cosmic radiation.

The NCI also noted that for certain subcategories of the population, the thyroid dose was probably substantially higher than the average for the area in which they lived. Children between the ages of 3 months and 5 years received doses that exceeded the average by a factor of 3–7, and individuals who drank unprocessed milk or goat's milk shortly after the tests also received substantially higher doses.

The conclusions were drawn from 14